8. **(Amended)** A method according to claim 7, wherein [~~in which~~] the coactivator is selected from ~~the group consisting of~~ RIP 140, SRC-1, TIF2, CBP, p300, TIF1, Trip1, Trip2, Trip3, Trip4, Trip5, Trip8, Trip9, p/CIP, ARA70 & Trip230.

9. **(Amended)** A method according to any one of claims 1, 3, 4, or 23 ~~and 5~~, wherein ~~in which~~ the transcription factor is a steroid hormone receptor.

10. **(Amended)** A method according to claim 9, wherein ~~in which~~ the steroid hormone receptor is selected from ~~the group consisting of~~ oestrogen receptor, progesterone receptor, androgen receptor and glucocorticoid receptor.

11. **(Amended)** A method according to claim 10, wherein ~~in which~~ the steroid hormone receptor is oestrogen receptor.

12. **(Amended)** A method according to any one of claims 1, 3, 4, or 23 ~~and 5~~, wherein the method is ~~in the form of~~ a 2-hybrid assay ~~system~~.

13 **(Amended)** A method according to any one of claims 1, 3, 4, or 23 ~~and 5~~, wherein the potential inhibitor compound is a member ~~in the form~~ of a peptide library based on the ~~a~~ signature motif ~~as defined in said claim~~.

23. **(New)** A method according to claim 1, wherein the fragment of a nuclear protein comprises only one signature motif.

REMARKS

Claims 1-13 are pending claims in the present application, and claims 1-4 and 7-13 are currently under consideration. Claims 14-22 are withdrawn from further consideration as being drawn to a nonelected invention or species. Applicants add new claim 23. Support of the subject matter of this new claim is found throughout the application. No new matter has been entered. Applicant will cancel non-elected claims upon indication of allowable subject matter. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note with appreciation that the response filed November 13, 2001, has been entered.

2. Regarding claim 5-6, the Examiner deemed them as being drawn to a nonelected invention or species without allowable generic or linking claims and thus withdrawn from further consideration. Applicants note that claim 1 is a generic claim linking elected and non-elected species. Claims 5 and 6 are dependent claims of claim 1, including all limitations of the generic claim 1. Pursuant to MPEP 809.04, "[i]f a linking claim is allowed, the examiner must thereafter examine species if the linking claim is generic thereto, or he or she must examine the claims to the non-elected inventions that are linked to the elected invention by such allowed linking claim." Thus, restrictions imposed on species encompassed by generic claims must be withdrawn upon indication of an allowable generic claim (MPEP 809). In other words, upon the allowance of a generic claim, Applicants are entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141 (MPEP 809.02(a)).

Furthermore, the burden is on the Examiner to examine these generic claims throughout their scope, together with any claims dependent thereon drawn to non-elected species or inventions, rather than for Applicants to limit the scope of the generic claims to conform to the scope of any species or inventions listed in a Restriction Requirement.

3. The disclosure is objected to due to an informality that the Brief Description of Drawing is absent from the specification. Applicants note that although a proper heading is absent, the content of the Brief Description of the Drawings is present in the specification (page 10-13). Accordingly, Applicants have amended the specification to include a heading of "Brief Description of the Drawings" which are believed to obviate the Examiner's objection. Reconsideration and withdrawal of this objection is respectfully requested.

4. Claims 1-4 and 7-13 are rejected under 35. U.S.C. §112, first paragraph, for allegedly failing to convey to one skilled in the art that applicants had possession of the claimed invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

The standard for assessing compliance with the written description requirement has been outlined in detail by the Guidelines for the Examination of Patent Applications which indicate that possession of the invention can be demonstrated in many ways, including "by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention."

The Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559, 1997 U.S. App. LEXIS 18221, 43 U.S.P.Q.2D (BNA) 1398 (Fed. Cir. 1997)) supports our position. In this case, the Federal Circuit addressed the question of how to adequately describe a genus of materials. In outlining what constitutes an adequate description of a genus with respect to genetic material, the court asserted that adequate description requires more than the gene or protein name.

> "[A] cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the DNA. See Fiers, 984 F.2d at 1171, 25 U.S.P.Q.2D (BNA) at 1606. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus **or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."** (emphasis added) 119 F.3d at 1566

Accordingly, for the description of a genetic invention to be deemed adequate to describe the genus that the claims encompass requires either a recitation of the structure (i.e., sequence) of a representative number of members of the genus **or** a recitation of the common features of the members of the claimed genus. This "recitation of structural features common to the members of the genus" is analogous to the way in which chemical genera are described, and provides features which readily allow one of skill in the art to recognize the claimed invention. This is in contrast to the way in which the claimed subject matter was recited in Lilly, where nucleic acids were claimed by the name of the cDNA and its origin, without any recitation of sequence or common structural or functional characteristics that could be used by one of skill in the art to readily envision the claimed sequences.

> "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." 119 F.3d at 1566

Applicants submit that the pending claims define the claimed subject matter in terms of generic formulae that indicate with specificity what the generic claims encompass, and accordingly meet the guidelines set forth above and comply with the written description requirement.

To better understand the present invention, a brief explication of the invention is provided below, with reference to Exhibits 1-2 (enclosed).

Turning first to Exhibit 1, it was appreciated that a ligand (e.g., oestrogen) binding to a nuclear receptor (e.g., oestrogen receptor) led to receptor dimerisation and effects on gene transcription in the nucleus. However, this process requires nuclear proteins ("bridging factors") to form part of the transcription initiation complex (see Exhibit 1). Interaction between a nuclear receptor and a nuclear protein is a protein-protein interaction, with potential interaction over a large surface area of the proteins involved. Applicants have identified a small signature motif on the nuclear protein which is an important structural element involved in binding to a nuclear receptor (see Exhibit 2). Applicants have shown that this small signature motif is both necessary and sufficient to mediate the binding of nuclear proteins to liganded nuclear receptors. Furthermore, through mutational analysis of the signature motif (Example 2, page 15), Applicants have delineated the sequence constraints of the signature motif on its functional interaction with nuclear receptors. For example, mutated signature motifs with one of the three leucine residues changed into alanine resulted in a complete loss of binding to the oestrogen receptor (ER), a nuclear receptor (Example 2, page 15; Figure 1B). This demonstrates that each

of the three leucine residues in the signature motif LXXLL is important for its function to interact with a nuclear receptor. Applicants have also shown that this motif is conserved throughout a large class of nuclear proteins (Example 3, page 1516; Figure 3A). Comparison of the signature motifs present in these nuclear proteins demonstrate that all three leucines in the motif are highly conserved.

It is highly surprising that this small signature motif is conserved throughout a large class of nuclear proteins. Indeed a commentator on the field stated, even after the priority date of the present invention, that *"characterizing the mechanisms by which nuclear factors engage the transcriptional apparatus in response to hormonal stimulation has seemed, at times, to be an insurmountable task"* (Marc Montminy in Nature, 12th June, 1997, 387, 654-655, see 1st paragraph thereof).

The discovery of signature motifs by the inventors Heery and Parker was published in the prestigious scientific journal Nature, 12th June, 1997, 387, 733-736 (enclosed as Exhibit 3). The last sentence of the abstract reads:

> "We propose that **the LXXLL motif is a signature sequence** that facilitates the interaction of different proteins with nuclear receptors and **is thus a defining feature** of a new family of nuclear proteins". (emphasis added)

This statement withstood rigorous peer review, indicating a significant contribution to the art made by the Applicants. Given Applicants' detailed disclosure of the signature motif as a "defining feature" of the nuclear proteins recited in the claims, Applicants submit that one of skill in the art can readily envision the claimed subject matter. Accordingly, Applicants submit that based on both the Guidelines for the Examination of Patent Applications, and the recent holdings of the Federal Circuit, Applicants have satisfied the requirements under 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of this rejection is respectfully requested.

5. Claims 1-4 and 7-13 are rejected under 35 U.S.C. §112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

To expedite prosecution, Applicants have amended the claims to more explicitly point out the claimed subject matter. Regarding claim 1, Applicants note with appreciation the

Examiner's recommendations regarding the recitation of the term "placing in contact", the removal of important limitations from the preamble and placing them into the method steps, and the deletion of the language "defined in this claim in b) above" in claim 1, and have adopted these suggestions in the amended claim 1. Applicants submit that these amendments do not narrow claim 1.

Regarding claim 7, 9, 12 and 13, Applicants note with appreciation the Examiner's recommendation regarding changing the language "any one of claims 1, 2 and 5" to "any one of claims 1, 2, or 5" in these claims, and have adopted these suggestions in the amended claims. Applicants submit that the amendments do not narrow the claims.

Regarding claim 13, the Examiner objected that the use of "potential inhibitor" lacks positive antecedent basis because "potential inhibitor compound" is what was recited earlier in the claims. Accordingly, Applicants have amended claim 13 to change "potential inhibitor" to "potential inhibitor compound". Applicants submit that this amendment does not narrow claim 13.

Applicants' amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of these rejections are requested.

Regarding claim 12, the Examiner objected that the use of "wherein the method is in the form of a 2-hybrid assay system" renders the claim vague and indefinite without a positive recitation of how the method steps in the base claims are individually further limited. Applicants respectfully submit that the "2-hybrid assay" is a term of art well understood and clear to a person with ordinary skill in the art. Support is provided by a review article by Fields *et al.* 1994 (enclosed as Exhibit 4). Reconsideration is requested.

7. Claims 1-4 and 7-13 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Chambon *et al.* ("the Chambon patent"), which relates to TIF-2, a nuclear protein bridging factor. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

The priority date for the present invention is April 30, 1997, earlier than the filing date of the Chambon patent, which is July 11, 1997, but later than the priority date for Chambon, which is July 12, 1996. Since Applicants' priority document provides support for subject matters that are allegedly anticipated by Chambon, Applicants submit that Chambon's priority document is the only allegedly relevant 102(e) prior art document for the present invention. A copy of the priority document for Chambon (US 60/021,247, filed: 7/12/1996) is enclosed as Exhibit 5.

Claim 1 of the present invention recites an important feature of the invention, *i.e.* "a fragment of a nuclear protein, wherein the fragment comprising a signature motif". The priority document for Chambon states at page 22, line 13 onwards, that for a TIF-2 fragment to interact with nuclear receptors in an agonist dependent manner and enhance nuclear receptor-mediated transcription activation, such TIF-2 fragment "should at least include amino acid residues 624-1287". Thus, one of ordinary skill in the art will understand that the fragment needs to be at least 664 amino acids and according to our analysis this fragment of TIF-2 contains 4 signature motifs: LLQLL at 641-645, LHRLL at 690-694, LRYLL at 745-749, and LGRLL at 878-882. Therefore, this description in Chambon leads to nothing more than an unwitting disclosure of a TIF-2 fragment which has been disclaimed from the amended claims set enclosed herein. Furthermore, new claim 23 specifically recites that the nuclear protein fragment comprises only one signature motif.

Applicants submit that narrowing Claim 1 by excluding the TIF-2 fragment 624-1287 from the claimed nuclear protein fragment is appropriate. *In re Johnson*, 558 F.2d 1008, 194 U.S.P.Q. 187 (C.C.P.A. 1977) is authority for the proposition that if an applicant has a genus and some species, he or she ought to be able to claim the genus excluding the disclosed species. In that case, the CCPA has held that the only inquiry is whether the original disclosure satisfied §112, first paragraph, for the limited genus later claimed. As discussed earlier, Applicants submit that our disclosure has satisfied the requirements under §112, first paragraph, for the entire genus of nuclear proteins fragments comprising a signature motif, exclusive of the TIF-2 fragment 624-1287.

The Chambon patent does contain a disclosure of an LXXLL motif (see SEQ ID NO 12). However, Applicants submit that Chambon is not entitled to its earliest priority date for this subject matter. The priority document for the Chambon patent contains no SEQ ID NO: 12 (the

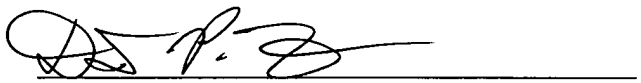
LXXLL motif) and has only two examples on Cloning/Expression of TIF-2 and Production of Antibodies thereto (compared with 7 Examples in the Chambon patent itself). Specifically, Example 3 of the Chambon patent, which discusses the LXXLL motif, is not in the priority document. Accordingly, the priority document for Chambon contains no disclosure of any motif in TIF-2 responsible for binding to nuclear receptor, let alone any disclosure of a short signature motif conserved through a diverse range of nuclear proteins. In contrast, Applicants' priority document for the present invention supports the claimed invention; see for example, Examples 1-8 and Figure 3A of the priority document.

Therefore, the claimed invention (as amended) is novel over Chambon. Reconsideration and withdrawal of the rejection are requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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